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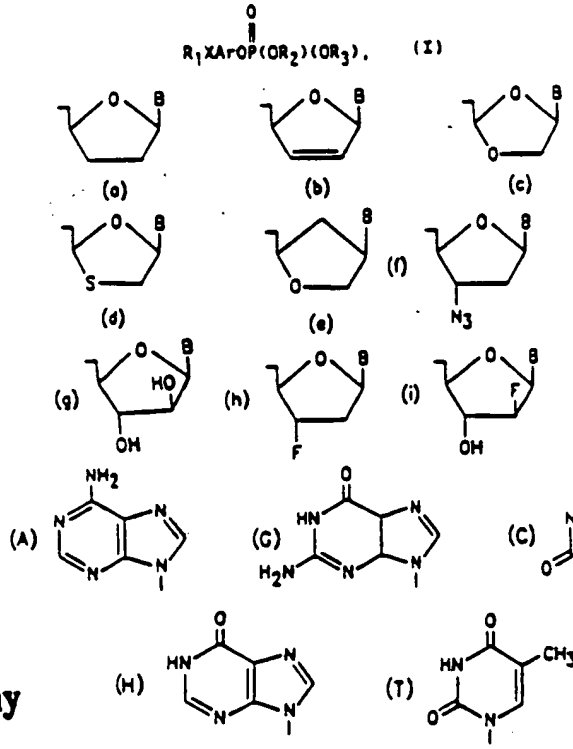
(54) Title: ANTIVIRAL COMPOUNDS

(57) Abstract

Compounds of formula (I) or a pharmaceutically acceptable salt thereof, in which R_1 represents an aliphatic hydrocarbyl group; Ar represents a substituted or unsubstituted aromatic nucleus; X represents $-SO_2-$ or $-CO-$ and R_2 and R_3 which may be identical or different represent moieties of formula (a), (b), (c), (d), (e), (f), (g), (h) or (i), wherein B represents the residue of a nucleoside base of formula (A), (G), (C), (H) or (T), provided that when R_2 and R_3 both represent an unsubstituted moiety of formula (a), B represents the residue of a nucleoside base which is of formula (A), (G), (C) or (H) are of value for their antiviral activity.

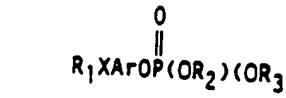


ANTIVIRAL COMPOUNDS

This invention relates to antiviral compounds, the use thereof, processes for the production of such compounds and intermediates useful in such processes.

Whilst the antiviral compound azidothymidine (AZT) is used clinically to combat the Human Immunodeficiency Virus (HIV) it suffers from drawbacks, for example, toxicity to bone marrow cells. Compounds have now been found which offer the promise of reduction in such toxicity.

Accordingly, the present invention comprises a compound of formula I or a pharmaceutically acceptable salt thereof (e.g. a hydrochloride):

I 

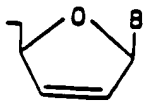
in which formula R_1 represents an aliphatic hydrocarbyl group e.g. an alkyl group which is preferably a C_1-C_6 alkyl group;

Ar represents a substituted or unsubstituted aromatic nucleus;

X represents $-SO_2-$ or $-CO-$ and

R_2 and R_3 which, though usually identical may be different represent moieties of formula (a), (b), (c), (d), (e), (f), (g), (h) or (i):

(a)



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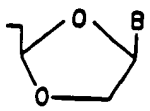

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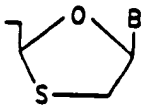

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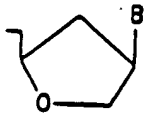

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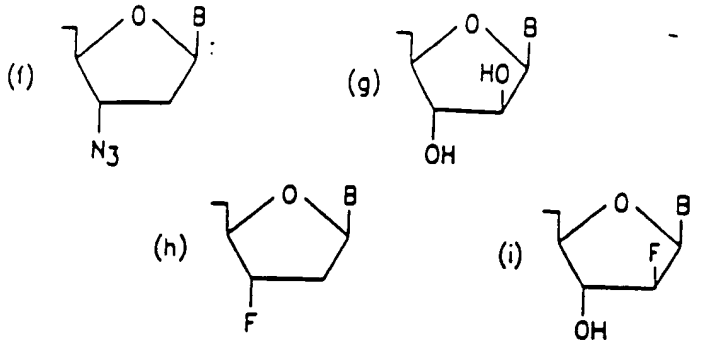
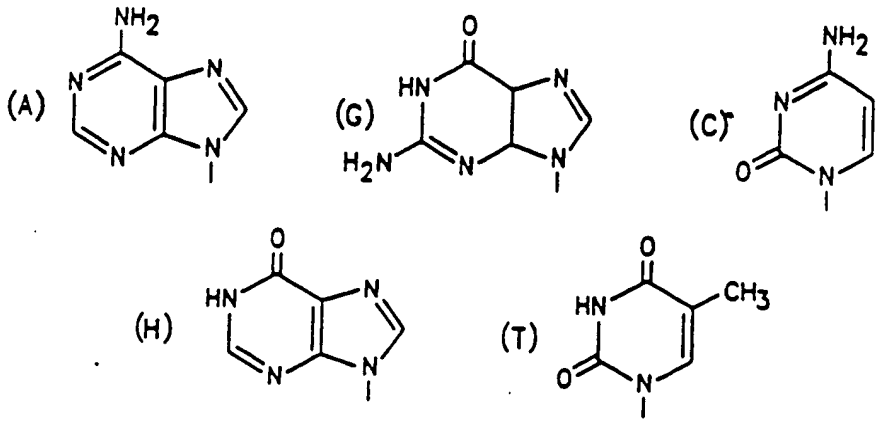


wherein B represents the residue of a nucleoside base of formula (A), (G), (C), (H) or (T):



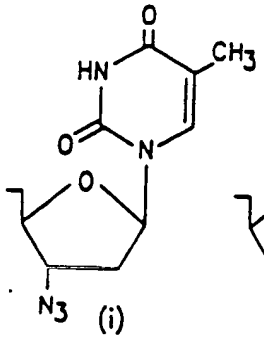
provided that when R_2 and R_3 both represent an unsubstituted moiety of formula (a) B represents the residue of a nucleoside base which is of formula (A), (G), (C) or (H). It will be appreciated that (A), (G), (C), (H) and (T) represent the residues respectively of adenosine, guanine, cytosine, hypoxanthine and thymine.

Typically, Ar represents a benzene ring in which the relative disposition of the group R_1X and phosphate substituents is mutually para, the ring usually carrying no further substituents.

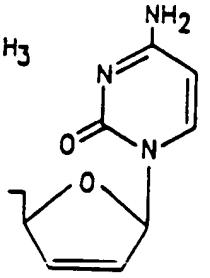
When, however, Ar represents a substituted aromatic nucleus, each substituent present is generally such that the compound hydrolyses readily to a corresponding phenol, R_1XArOH which is not intolerably toxic.

Though Ar preferably represents an unsubstituted benzene ring, up to four substituents may be carried on the nucleus, those of particular interest including halogen e.g. chlorine, fluoroalkyl e.g. trifluoromethyl, difluoromethyl, monofluoromethyl, alkoxy e.g. C_1-C_4 alkoxy, fluoroalkoxy, carboalkoxy e.g. C_1-C_6 carboalkoxy, amino, and amido. The alkyl group R_1 is generally unbranched and is typically a methyl group and X preferably represents a sulphonyl group.

Moieties R_2 and R_3 of especial interest include: (i) -(x) and particularly (i), (v), (vi) and (ix).



(i)



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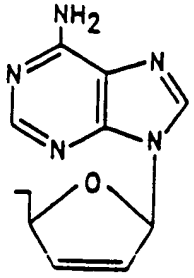

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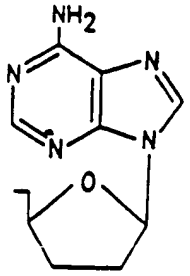

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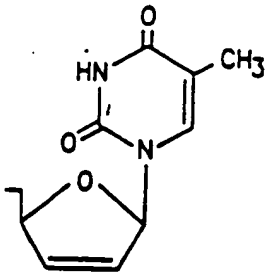

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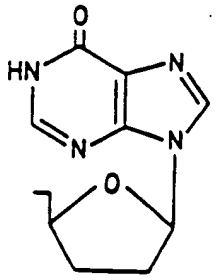

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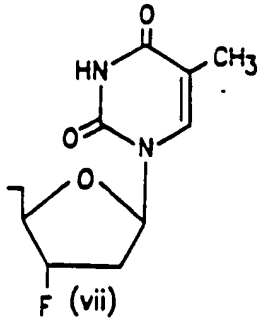

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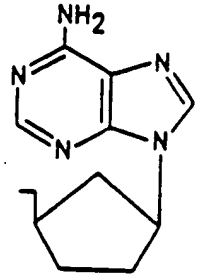

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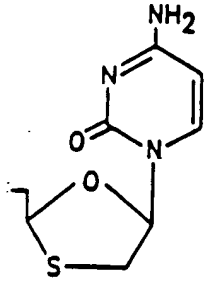

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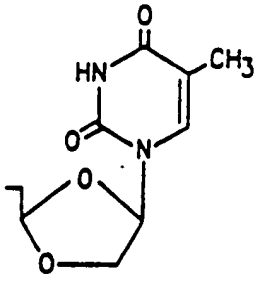


(x)

It will be appreciated that the moieties (i) -(vi) are found in compounds which may be represented by abbreviated nomenclature as (i) AZT, (ii) d^4C, (iii) d^4A, (iv) d^2A, (v) d^4T, (vi) ddI.

Compounds of the present invention may be produced in accordance with a further aspect thereof by reaction between a phosphorodihalidate of formula III: $R_1XArOP(O).Y_2$ (wherein Y represents halogen, e.g. chlorine) and a compound of formula R_2OH (e.g. azidothymidine) or a derivative thereof e.g. a derivative in which a group in the nucleoside base is protected, as may be the free amino group in cytosine, by acetylation. The reaction is usually conducted in the presence of a base e.g. 1-methylimidazole and is typically conducted in an aprotic solvent such as acetonitrile.

Alternatively, when X represent SO_2, compounds of formula I may be produced in accordance with a further aspect of the present invention by oxidation of a compound of formula IV: $R_1SArOP(O)(OR_2)(OR_3)$ or of formula (V): $R_1SOArOP(O)(OR_2)(OR_3)$, oxidation typically being carried out with a per acid such as 3-chloroperbenzoic acid.

The present invention further includes within its scope intermediates of formula IV and formula V.

Compounds of the present invention find application in the treatment or prophylaxis of human retrovirus infections and particularly Human Immunodeficiency Virus (HIV) infection which gives rise to Acquired Immune Deficiency Syndrome (AIDS).

Accordingly, in a further aspect the invention comprises a compound of formula I for use in therapy and in a yet further aspect of the present invention the use of a compound of formula I for the manufacture of a medicament useful in the treatment or prophylaxis of a human retrovirus infection, particularly HIV, or of Acquired Immuno Deficiency Syndrome.

The dosage form and amount can be readily established by reference to known treatment or prophylactic regimens. In general however the dosage of the compound of formula I will be lower than the corresponding amount of AZT and usually lies

within the range about 50 to about 800 mg.

While it is possible for the active compound of formula I or pharmaceutically acceptable salt thereof to be administered alone, it is preferable to present the active compound as a pharmaceutical formulation. Formulations of the present invention, for medical use, comprise the active compound together with one or more pharmaceutically acceptable carriers thereof and, optionally, any other ingredients which may be therapeutic per se, synergistic with the compound of formula I, or both. Carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present invention therefore further provides a pharmaceutical formulation comprising a compound of formula (I) (in the form of the free base or a pharmaceutically acceptable acid addition salt) together with a pharmaceutically acceptable carrier thereof.

The formulations include those suitable for oral, rectal, topical or parenteral (including subcutaneous, intramuscular and intravenous) administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include generally the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. Usually, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or with a finely divided solid carrier or with both and then, if necessary, shaping the product into desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a suspension in an aqueous liquid or non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught. The

active compound may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active compound in a free-flowing form such as a powder or granulas, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active compound with any suitable carrier.

A syrup may be made by adding the active compound to a concentrated, aqueous solution of a sugar, for example sucrose, to which may be added any accessory ingredient. Such accessory ingredient(s) may include flavourings, an agent to retard crystallisation of the sugar or an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol for example glycerol or sorbitol.

Formulations for rectal administration may be presented as a suppository with a usual carrier such as cocoa butter.

Formulations suitable for parental administration conveniently comprise a serile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient.

In addition to the aforementioned ingredients, formulations of this invention, for example ointments, creams and the like, may include one or more accessory ingredient(s) selected from diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

The present invention is illustrated by the following Example:

Example 1

Preparation of 4-(methylsulphonyl)phenyl bis (3'-azido thymidin-5'-yl) phosphate

A. 4-(Methylsulphonyl)phenyl phosphorodichloridate.

4-(Methylthio)phenyl phosphorodichloridate. To a solution of

freshly distilled phosphoryl chloride (45 ml, 0.5 mol) and 1-methylimidazole (0.15 ml), is added 4-(methylthio)phenol (14, 0.1 mol) and the solution is heated under reflux for 20 h. The excess of phosphoryl chloride is removed by distillation and the residue distilled under reduced pressure to give the product (11 g, 42% yield); bp 135-142°C (2 mm Hg) ^{1}H NMR ($CDCl_3$) δ 2.39 (3H, s, SCH_3), 7.22 (4 H, s, phenyl).

4-(Methylsulphonyl)phenol. To a solution of 4-(methylthio)-phenol (7.0 g, 0.05 mol) in 30% aqueous methanol (100 ml) at 0°C is added a solution of sodium periodate (10.7 g, 0.05 mmol) and the resulting suspension is stirred for 30 min. Water (500 ml) is then added and the precipitate removed by filtration. The filtrate is cooled to 4°C and a further portion of sodium periodate (10.7 g, 0.05 mmol) added and the resulting suspension stirred for 48 h when a further portion of sodium periodate (5.35 g, 0.025 mmol) is added. After stirring for a further 18 h, the precipitate is removed by filtration, the filtrate extracted with ether which is evaporated to dryness and the residue is purified on a silica column using chloroform methanol, 9:1, as eluent to give the title compound (2.75 g, 32% yield). Anal. ($C_7H_8O_3S$), C,H.

4-(Methylsulphonyl)phenyl phosphorodichloridate. 4-(Methyl-thio)phenol (3.0 g, 17 mmol) is heated under reflux with freshly distilled phosphoryl chloride (13.35 ml, 87 mmol) and 1-methylimidazole (0.05 ml) for 20 h. The excess of phosphoryl chloride is removed by distillation and the residue is distilled under reduced pressure to give the title compound (bp 185°C, 1 mm Hg) as a yellow oil which solidifies on cooling (500 mg, 10% yield). Anal. (free acid $C_7H_9O_6S$) C,H.

B. 4-(methylsulphonyl)phenyl bis (3'-azidothymidin-5'-yl)-phosphate.

4(methylsulphonyl)phenyl phosphorodichloridate (52mg 0.18 mmol), 1-methylimidazole (0.08ml 0.92mmol) and dry acetonitrile (3ml.) are stirred for 5 minutes at room temperature under dry nitrogen. The addition of Azido thymidine (80mg 0.3mmol) in 1ml

of dry acetonitrile follows. The resulting suspension is then stirred overnight at room temperature. Thin Layer Chromatography (Tlc) of the reaction mixture shows only ca. 25% of the slower moving spot in $CHCl_3$:MeoH (9:1). At this stage another equivalent of 4-(methylsulphonyl)phenyl phosphorodichloridate and 1-methylimidazole in dry acetonitrile is added and the reaction mixture is stirred for a further 48 hours. Tlc then shows ca. 90% conversion to the slower moving component. After addition of phosphate buffer (15ml. pH6.0) the mixture is extracted with chloroform (4 x 10ml). The chloroform extracts are washed with water and then dried over magnesium sulphate. The chloroform is evaporated under reduced pressure and the residue is applied, pre-absorbed onto silica gel. to a short silica gel column (80g, type 7734). The column is eluted with chloroform : methanol (9:1). The appropriate fractions are concentrated to give a white solid (115mg., 52%).

NMR Spectra:

(^1H)δ(d_6DMSO): 11.36(2H,S,NH), 7.95(2H,d,phenyl) 7.55(2H,d,H-6), 7.45(2H,d,phenyl), 6.14(2H,t,-H-1^1), 4.45(2H,m,H-3^1), 4.04(2H,m,H-4^1), 3.42(4H,m,H-5^1), 3.21(3H,S,SO_2CH_3) 2.44(4H,m,H-2^1), 1.71(6H,S, CH_3)

Elemental Analysis:

Found: C, 42.9; H, 4.5; N, 18.9; $C_{27}H_{31}N_{10}O_{12}P5$ requires C, 43.2; H, 4.16; N, 18.66.

Mass Spectrum:

M/Z 751 $(M+H)^+$. 773 $(M+Na)^+$.

Example 2

Preparation of 4-(Methylsulphonyl)phenyl bis (3-azido thymidin-5'-yl)phosphate via 4-(methylthio)phenyl analogue.

4-Methylthio)phenyl bis (3'-azidothymidin-5'-yl) phosphate (144 mg, 0.2mmol, prepared by reaction of 4-(methylthio)phenyl phosphorodichloridate (Example 1A) with azido thymidine) is dissolved in dry ethanol and cooled to 0°C. A solution of 3-chloroperoxybenzoic acid (107mg, 0.6 mmol) in dry ethanol (15ml) is added dropwise with stirring over 15 minutes. The

resulting solution is stored overnight at 5°C. After this period, Tlc (chloroform-methanol (9:1)) shows ca. 90% conversion to a slower-moving component. The solvent is evaporated under reduced pressure and the residue is applied, pre-absorbed onto silica gel, to a silica gel column (10g, type 9385). The column is eluted with chloroform-methanol (9:1). The appropriate fractions are concentrated and purified further using the chromatotron (2mm plate, same solvent system). The product is isolated as a white solid (105mg. 70%).

A sample of the compound 4-(methylsulphonyl)phenyl bis 3'-azidothymidin-5'-yl phosphate is shown by HPLC analysis in reverse phase chromatography to consist of 4 components : azidothymidine (AZT) as a minor component, 4-(methylsulphonyl) phenyl bis 3' azidothymidin-5'-yl phosphate, the latter compound without the side chain on the ester linkage and an unidentified component.

The sample, considered of adequate quality for antiviral testing is assayed as follows:

Anti-HIV Testing

The assays are carried out in 96 well (microtitre) panels using the MT4 cell line, infected with IOTCID50 of HIV 3B. The antiviral activity and cytotoxicity of each compound is assayed simultaneously. Three compounds are screened on each panel. Each compound is tested at 100.0, 10.0, 1.0 and 0.1μM, unless otherwise stated. AZT is included in each assay as a positive control at 10.0, 1.0, 0.1 and 0.01μM.

The antiviral activity (in infected cells) and cytotoxicity (to uninfected cells) of each compound is determined by measuring the number of viable cells remaining after 5 days incubation of 37°C and comparing them with infected or uninfected controls. The number of viable cells is determined by the addition of the tetrazolium dye MTT. MTT uptake and conversion to a blue Formazan derivative has been shown to be linear with viable cell number. Following MTT addition, the cells are solubilised with acidified isopropanol and the extent of MTT conversion is

measured spectrophotometrically.

Antiviral activity is apparent through the ability of compounds to protect the cells from virus induced cytopathic effect. The result is reported as the percentage of cells protected at a given drug concentration.

The results of the assay are shown in the Table

TABLE

	% Protection						
Concentration of BTG 1704:	100	10	1.0	0.1	0.01	0.001µM	MTC
Antiviral Activity:	13%	79%	91%	91%	21%	9%	100µM

It can be seen from the table 1 that concentrations of BTG 1704 between 0.1 and 10µM offers significant protection of MT4 cells from HIV-1 cytopathic effect. The toxic concentration of the drug is estimated to be about 100µM. This is not however a quantitative test for cytotoxicity.

Example 3

4-(Methylsulphonyl)phenyl bis (2',3'-didehydro-2',3'-dideoxy cytidin-5'-yl)phosphate

N^4-acetyl-2',3'-didehydro-2',3'-deoxycytidine: 2',3'-dide-hydro-2',3'-dideoxycytidine (36.2 mmol) is suspended into dry methanol (10000ml) and heated to reflux. Dry acetic anhydride (10 ml, 106 mmol) is added 4 times at every hour (total amount 40 ml, 0.42 mol). The reaction mixture is finally stirred for 6 hr. at refluxed temperature and then left overnight at room temperature. The precipitated crystal is filtered out and washed with ethanol. (73% yield).

4-(Methylthio)phenyl bis (N^4-acetyl-2',3'-didehydro-2',3'-dideoxycytidin-5'-yl)phosphate

4-(methylthio)phenyl phosphorodichloridate, dry 1-methyl-imidazole and dry acetonitrile are stirred vigorously for 5 min. and then added to a solution of N^4-acetyl-2',3'-didehydro'2',-3'-dideoxycytidine in acetonitrile. After stirring for several

hours at room temperature, phosphate buffer is added (pH 6.0) and the mixture is extracted with chloroform. The chloroform extracts are washed with water and then dried over magnesium sulphate. The chloroform is evaporated under reduced pressure and the residue is applied, pre-absorbed, onto silica gel, to a short silica gel column. The column is eluted and the resulting material is further purified using a chromatotron (2 mm plate). The product is then isolated.

4-(Methylthio)phenyl bis (2',3'-didehydro-2',3'-dideoxy-cytidin-5'-yl)phosphate

4-(Methylthio)phenyl bis(N^4-acetyl-2',3'-didehydro-2',3'-dideoxycytidin-5'-yl)phosphate is stirred with potassium carbonate/methanol solution for 20 hrs. at room temperature. After this period the solvent is evaporated under reduced pressure and the residue is applied, pre-absorbed, onto silica gel, to a short silica gel column. The column is eluted and the product is isolated.

4-(Methylsulphonyl)phenyl bis(2',3'-didehydro-2',3'-dideoxycytidin-5'-yl)phosphate

4-(Methylthio)phenyl bis(2',3'-didehydro-2',3'-dideoxycytidin-5'-yl)phosphate is dissolved in dry ethanol and cooled to 0°C. A solution of 3-chloroperoxybenzoic acid is added dropwise with stirring over 10 min. and the mixture is stored for 15 hrs. at 5°C. After this period, TLC shows complete conversion of starting material to a major component together with a minor impurity. The solvent is removed by evaporation under reduced pressure and the residue is applied to a 2 mm chromatotron plate in a small volume of chloroform, and then eluted. This purification step is repeated and the product is isolated.

Example 4

4-(Methylsulphonyl)phenyl bis(2',3'-didehydro-2',3'-dideoxy-adenosin-5'-yl)phosphate

4-(Methylsulphonyl)phenyl phosphorodichloridate (86 mg, 0.3 mmol), dry 1-methlyimidazole (0.13 ml, 1.4 mmol) and dry pyridine (20 ml) are stirred for 5 min. and then added to

2',3'-didehydro-2',3'-dideoxyadenosine (100 mg, 0.4 mmol). The reaction mixture is stirred vigorously for 18 hrs. at room temperature. T.l.c. shows ca. 50% conversion of starting material to a slower-moving component. A further portion of "phosphorylating agent" (86 mg, 0.3 mmol and 0.13 ml, 1.4 mmol 1-methylimidazole) is added and the reaction is again stirred for 24 hours. After this period, t,l,c shows still ca. 50% conversion to the slower-moving component. The reaction mixture is evaporated to dryness under reduced pressure. The residue is applied, pre-absorbed onto silica gel, to a silica gel column and eluted with chloroform:methanol (10:1). The required fractions are collected and evaporated to dryness, and then dissolved in a minimum of chloroform and triturated with addition of hexane to give the product (23 mg, 16% yield).

NMR Spectrum: $\delta(d_6DMSO)$ 3.19(3 H, s, SO_2CH_3), 4.24 (2 H, s, 2x H-5'), 5.04 (2 H, s, 2x H-4'), 6.26 (2 H, t, 2x H-1'), 6.42 (2 H, s, 2x H-3', 6.96 (2 H, s, 2x H-2'), 7.32 (4 H, d, 2x NH_2), 7.22-7.77 (4 H, dd, phenyl), 8.07 (2 H, d, 2x h-2), 8.16 (2 H, s, 2x H-8)

FAB Mass Spectrum: m/z 683 $[M + H]^+$

Example 5

4-(Methylsulphonyl)phenyl bis(2',3'-dideoxyadenosin-5'-yl) phosphate

4-(Methylsulphonyl)phenyl phosphorodichloridate (87 mg, 0.3 mmol), dry 1-methylimidazole (0.13 ml, 1.4 mmol) and dry pyridine (20 ml) are stirred for 5 min. and then added to 2',3'-dideoxyadenosine (120 mg, 0.5 mmol). The reaction mixture is stirred for 16 hours at room temperature under a stream of nitrogen. T.l.c. shows ca. 40% conversion of starting material to a slower-moving component. A further portion of "phosphorylating agent" (87 mg, 0.3 mmol and 0.13 ml, 0.3 mmol 1-methylimidazole) is added and the reaction mixture is again stirred for 24 hours. The reaction mixture is evaporated to dryness under reduced pressure. The residue is applied, pre-absorbed onto silica gel, to a silica gel column

chromatography and eluted with dichloromethane:methanol (20:3).
NMR Spectrum: $\delta(d_6DMSO)$ 2.08 (4 H, m, 2x H-2'), 2.80 (4 H, m, 2x H-3'), 3.92 (4 H, m, 2x H-5'), 4.26 (2 H, s, 2x H-4'), 6.24 (2 H, m, 2x H-1'), 7.26 (4 H, s, 2x NH_2), 7.31-7.84 (4 H, m, phenyl), 8.13 (2 H, s, 2x H-2), 8.27 (2 H, s, 2x H-8).
FAB Mass Spectrum: m/z 687 $[M + H]^+$

Example 6

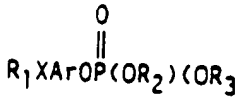
4-Methylsulphonyl)phenyl bis(2',3'-didehydro-2',3'-dideoxy-thymidin-5'-yl)phosphate

4-(Methylsulphonyl phosphodichloridate (58 mg, 0.2 mmol), dry 1-methylimidazole (85 µl, 1.0 mmol) and dry acetonitrile (5 ml) are stirred vigorously for 5 min. and then added to a solution of 2',3'-didehydro-2',3'-dideoxythymidine (70 mg, 0.3 mmol) in dry acetonitrile (5 ml). After stirring for 17 hours at room temperature under a stream of nitrogen, t.l.c. (chloroform:methanol=10:1) shows ca. 60% conversion to a slower-moving component. A further portion of "phosphorylating agent" (22 mg, 0.1 mmol and 0.4 ml, 0.4 mmol 1-methylimidazole) is added, and after stirring for 26 hrs., a further portion of "phosphorylating agent" (13 mg, 0.05 mmol and 0.4 ml, 0.4 mmol 1-methylimidazole) is added. The reaction mixture is stirred at 37°C for 18 hours, but t.l.c. shows the conversion of 60% is not improved at all. After addition of phosphate buffer (20 ml, pH 6.0), the mixture is extracted with chloroform. The organic layer is dried (magnesium sulphate), then evaporated to dryness under reduced pressure. The residue is purified by silica gel column chromatography with ether:methanol (5:1) as eluent to give the product (35 mg, 34% yield).
NMR Spectrum: $\delta(d_6DMSO)$ 1.65 (6 H, d, 2x CH_3), 3.25 (3 H, s SO_2CH_3), 4.35 (4 H, m, 2x H-5'), 4.95 (2 H, s, 2x H-4'), 6.05 (2H, m, 2x H-3'), 6.40 (2 H, m, 2x H-2'), 6.85 (2 H, s, 2x H-1'), 7.25-7.40 (4 H, dd, phenyl), 7.90 (2 H, m, 2x H-6), 11.35 (2 H, d, 2x NH).

FAB Mass Spectrum:	m/z 665 $[M + H]^+$
Elemental Analysis:	
Found:	C, 48.9 ; H, 4.6 ; N, 8.5
$C_{27}H_{29}O_{12}N_4PS$ requires	
	C, 48.8 ; H, 4.4 ; N, 8.4%.

CLAIMS

1. A compound of formula I or a pharmaceutically acceptable salt thereof :

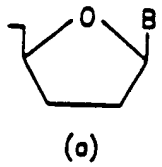
I 

in which formula R_1 represents an aliphatic hydrocarbyl group;

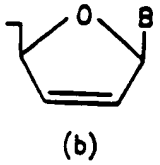
Ar represents a substituted or unsubstituted aromatic nucleus;

X represents $-SO_2-$ or $-CO-$ and

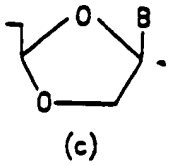
R_2 and R_3 which may be identical or different represent moieties of formula (a), (b), (c), (d), (e), (f), (g), (h) or (i):



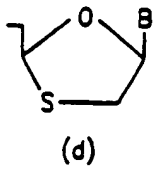
(a)



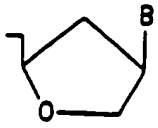
(b)



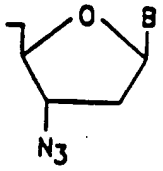
(c)



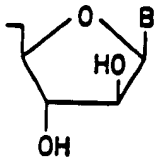
(d)



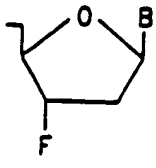
(e)



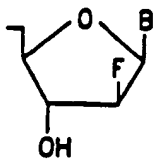
(f)



(g)

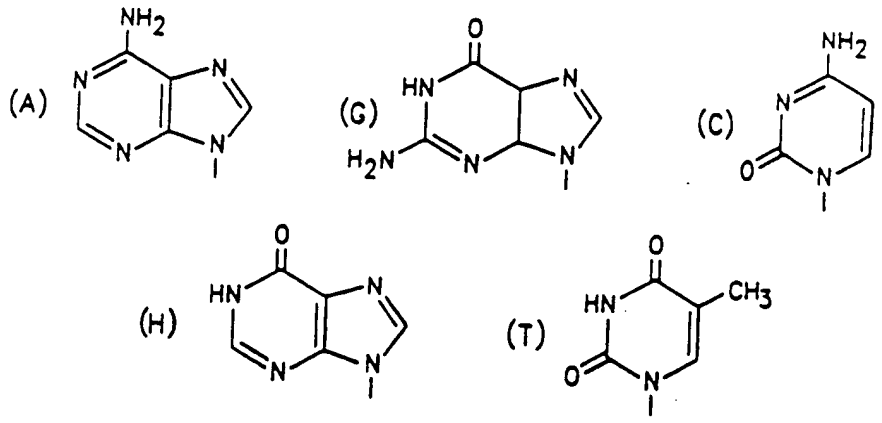


(h)



(i)

wherein B represents the residue of a nucleoside base of formula (A), (G), (C), (H) or (T):



provided that when R_2 and R_3 both represent an unsubstituted moiety of formula (a) B represents the residue of a nucleoside base which is of formula (A), (G), (C) or (H).

2. A compound according to Claim 1, in which Ar represents a substituted or unsubstituted benzene ring.

3. A compound according to Claim 2, in which the group R_1X and phosphate substituents have a mutually para disposition.

4. A compound according to Claim 1, in which Ar represents a substituted aromatic nucleus which is such that the compound I readily hydrolyses to a corresponding phenol R_1XArOH which is not intolerably toxic.

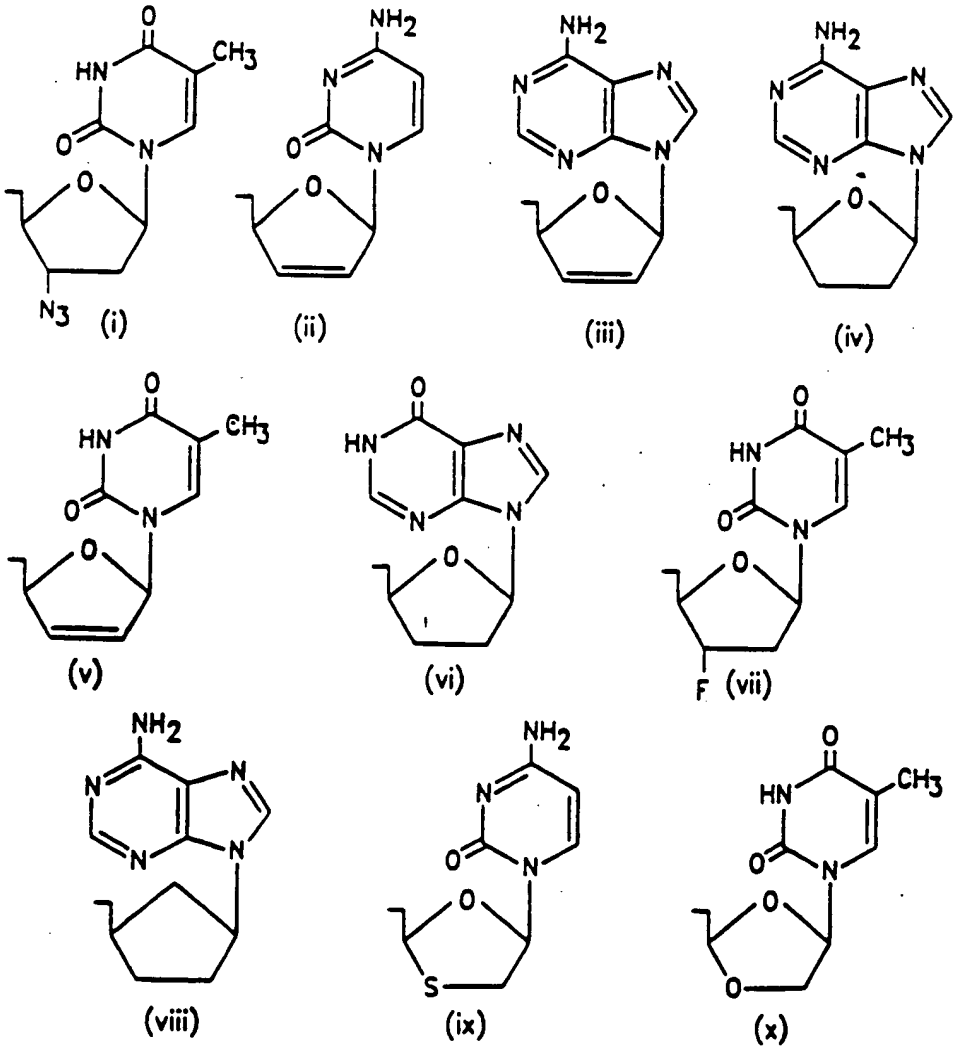
5. A compound according to Claim 1, in which A represents a benzene ring carrying one or more substituents which may be identical or different and which are halogen, fluoroalkyl, alkoxy, fluoroalkoxy, carboalkoxy, amino or amido.

6. A compound according to Claim 1 in which X represents a sulphonyl group.

7. A compound according to any preceding Claim, in which R_2 and R_3 independently represent moieties of formula (a), (b), (d), or (f).

8. A compound according to Claim 7, in which R_2 and R_3 independently represent the moiety of formula (f) as hereinbefore defined.

9. A compound according to Claim 7, in which R_2 and R_3 independently have any of the formulae (i) to (x):



10. A compound according to Claim 9, in which R_2 and R_3 independently represent formulae (i), (v), (vi) or (ix).

11. 4-(methylsulphonyl)phenyl bis (3'-azido thymidin-5'-yl) phosphate.

12. 4-(Methylsulphonyl)phenyl bis (2',3'-didehydro-2',3'-dideoxy cytidin-5'-yl)phosphate.

13. 4-(Methylsulphonyl)phenyl bis(2',3'-didehydro-2',3'-dideoxy-adenosin-5'-yl)phosphate.

14. 4-(Methylsulphonyl)phenyl bis(2',3'-dideoxyadenosin-5'-yl) phosphate.

15. 4-Methylsulphonyl)phenyl bis(2',3'-didehydro-2',3'-dideoxy-thymidin-5'-yl)phosphate.

16. A process for the production of a compound of formula I which comprises reacting a phosphorodihalidate of formula III

III: $R_1XArOP(O)Y_2$

in which formula:

R_1 represents an aliphatic hydrocarbyl group

X represents $-SO_2-$ or $-CO-$ and

Y represents halogen

with a compound of formula R_2OH, R_2 being as hereinbefore defined, or with a derivative in which a group in the nucleoside base of R_2 is protected.

17. A process according to Claim 16, in which the nucleoside base in R_2 is cytosine protected by acetylation.

18. A process according to Claim 16 or 17, in which the reaction is conducted in the presence of a base.

19. A process according to Claim 18, in which the base is 1-methylimidazole.

20. A process for the production of a compound of formula I, in which a compound of formula IV $R_1SArOP(O)(OR_2)(OR_3)$ or of formula V $R_1SOArOP(O)(OR_2)(OR_3)$ in which formulae R_1, Ar, R_2 and R_3 are as hereinbefore defined are subjected to oxidation.

21. A process according to Claim 20, in which oxidation is effected by a per acid.

22. An intermediate of formula IV as hereinbefore defined.

23. An intermediate of formula V as hereinbefore defined.

24. A compound of formula I as hereinbefore defined for use in therapy.

25. The use of a compound of formula I as hereinbefore defined for the manufacture of a medicament useful in the treatment or prophylaxis of a human retrovirus infection.

26. A method for the treatment or prophylaxis of a human retrovirus infection which comprises administering to an individual infected with the virus a compound of formula I in an amount effective to inhibit or prevent viral replication.

27. A method for the treatment or prophylaxis of a human retrovirus infection which comprises treating blood infected with the virus with a compound of formula I in an amount effective to inhibit or prevent viral replication.

28. A method according to Claim 26 or 27 in which the virus is Human Immunodeficiency Virus (HIV).

29. A formulation for the treatment or prophylaxis of a human retrovirus infection which comprises a compound of formula I together with a pharmaceutically acceptable carrier therefor.

30. A formulation according to Claim 29, in dosage form.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 90/00542

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 H 19/10, 19/20, A 61 K 31/70, C 07 F 9/6558, 9/6561

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System	Classification Symbols
IPC[5]	C 07 H 19/00 A 61 K 31/00, C 07 F 9/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
A	Chemical and Pharmaceutical Bulletin, volume 28, no. 10, October 1980, M. Saneyoshi et al.: "Synthetic nucleosides and nucleotides. XVI. Synthesis and biological evaluations of a series of 1-beta-D-arabino-furanosylcytosine 5'-alkyl or arylphosphates", pages 2915-2923 see abstract; page 2915, line 1 - page 2916, end	1,25,27
A	DE, A, 2009834 (SYNTEX CORP.) 17 September 1970 see claim 1; page 11, lines 6-14	1
A	EP, A, 0284405 (IVAX LABORATORIES INC.) 28 September 1988 see claims 1-8	1,25,27,29, 30

./.

* Special categories of cited documents: **

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29th June 1990	19.07.90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme N. KUIPER

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	Chemische Berichte, volume 108, no. 9, September 1975, A. Myles et al.: "Synthese und Eigenschaften von Thymidylyl-(3'→3')-, -(3'→5')-und-(5'→5')-thymidin", pages 2857-2871 see abstract; page 2860, compounds 4, 14-19; page 2861, lines 1-21; page 2870, line 7 - page 2871, end	1

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers * because they relate to subject matter not required to be searched by this Authority, namely:

* Claims searched incompletely: 28
Claims not searched : 26

See PCT-Rule 39.1(IV); Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9000542 SA 36027

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/07/90
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DE-A- 2009834	17-09-70	FR-A-	2034785	18-12-70
		GB-A-	1301182	29-12-72
EP-A- 0284405	28-09-88	AU-A-	1375888	29-09-88
		JP-A-	64003197	06-01-89

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